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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,077	09/26/2003	Gunars Valkirs	36671-743.502	7483

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

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06/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/673,077	VALKIRS ET AL.	
	Examiner	Art Unit	
	LISA V. COOK	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,8,11,14-16 and 18-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,8,11,14-16 and 18-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/4/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences (paper filed 4/4/08), but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 6/4/08 has been entered.

2. Currently claims 1, 5, 8, 11, 14-16, and 18-26 are pending and under consideration.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

4. The information disclosure statement filed 6/4/08 has been considered as to the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claim 1 recites the broad recitation "wherein the plurality of markers are independently selected from the group consisting of specific markers of neural tissue injury, markers related to blood pressure regulation, markers related to inflammation, and markers related to apoptosis, and the claim also recites that the "markers are selected from the group consisting of neural cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), B-type natriuretic peptide (BNP), NT-proBNP, matrix metalloprotease-9 (MMP-9), caspase-3, and von Willebrand factor (vWF), or markers related thereto", which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 1, 14, 16 and 19-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122).

Sviri et al. disclose methods for measuring brain natriuretic peptide (BNP) plasma concentrations in patients with aneurismal subarrachnoid hemorrhage (SAH). The purpose of the study was to investigate the relationship between BNP plasma concentrations and cerebral vasospasm (CVS) after anueurysmal SAH (Applicant's characterizing a risk of future CVS). The BNP plasma levels were also investigated with respect to neurological condition, SAH severity on CT, and flow velocity. See abstract.

The blood samples were collected for plasma and analyzed by a specific immunoradiometric assay (reading on claims 19-21). See page 119, 2nd column-blood tests.

The researchers found that BNP plasma levels are elevated shortly after SAH and increase markedly during the clinical course only in patients, with symptomatic CVS. See page figure 2, page 121, 2nd column, and 122 1st column, last paragraph. The specification discloses that BNP is a marker for blood pressure regulation. (For example, see page 77 of the disclosure).

Although Sviri et al. are silent with respect to the measurement of NT-pro BNP and pro-BNP, the measurement of BNP necessarily measures NT-pro BNP and pro-BNP because they all contain the same BNP sequence. Support for the reasoning can be found in the specification on page 29, for example. In considering the anticipatory effect of a reference, not only its specific teachings but also the inference which one skilled in the art would reasonably be expected to draw therefrom should be taken into account. In re Preda (CCPA 1968) 401 F2d825, 159 USPQ 342.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

II. Claims 22-24 are rejected under 35 U.S.C. 103(a) as being obvious over Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) in view of Jackowski (WO 00/52476).

Please see Sviri et al. as set forth above.

Sviri et al. differ from the instant invention in not specifically teaching the measurement of concentration threshold levels and determining temporal change.

However, Jackowski discloses methods for assessing stroke (brain or temporal change) via the measurement of multiple markers. These markers include calbindin-D, myeline basic protein, S-100β, and thrombomodulin. The detection of these markers can distinguish and/or differentiate between ischemic and hemorrhagic events.

On page 1, Jackowski discloses that stroke is routinely diagnosed with a CAT scans to assess brain damage. See lines 18-29. The multiple markers may be determined in the same sample or from samples obtained at different time periods. See page 12 lines 3-16. This allows for patient analysis and monitoring.

The detection of multiple markers can distinguish and/or differentiate between ischemic and hemorrhagic events. Threshold levels (normal and/or elevated levels) are taught on page 9, lines 12-20. Jackowski teaches that the method determines where the levels of all four markers are negative or within the normal range, there is no cerebral injury. When only brain endothelial membrane protein (i.e. thrombomodulin - Tm) is elevated or positive (at least 2 standard deviations above normal) the stroke is a lacunar infarct. When the NSE level is positive and the S100 and/or MBP levels are negative (the brain endothelial membrane protein marker is positive or negative) the patient has suffered a TIA.

This evaluation aids in patient treatment. Jackowski teaches the determination of a plurality of patient derived markers which are correlated to a subarrachnoid hemorrhage. See abstract, figure 2, and column 3-4, for example. See page 2 lines 11-22 and figure 2/6, for example.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate temporal changes via CAT scans and evaluate multiple markers at various threshold levels as taught by Jackowski et al. in the method of Sviri et al. because Jackowski et al. taught that the detection of multiple markers can distinguish and/or differentiate between ischemic and hemorrhagic events. This evaluation aids in patient treatment. See abstract, figure 2, and column 3-4, for example. See page 2 lines 11-22 and figure 2/6, for example.

One of ordinary skill in the art would have evaluated multiple marker and CAT in order to assess and monitor brain damage and aid in patient treatment.

III. Claims 5 and 15 are rejected under 35 U.S.C. 103(a) as being obvious over Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) in view of Ronn et al. (WO 00/18801).

Please Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) as set forth above.

Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) differ from the instant invention in not specifically teaching the detection of NCAM or neural cell adhesion molecule.

However, Ronn et al. disclose methods to determine and assess the NCAM marker. See abstract, page 16 lines 8-31, and page 34 lines 11-28. The marker is useful in the evaluation of several disorders including stroke. Absent evidence to the contrary, it would have been obvious to one of ordinary skill in the art to employ the marker NCAM to assess stroke because the prior art has established the relationship between NCAM and stroke. See WO 00/52476 to Ronn et al.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use NCAM as a marker for stroke, since it has been held to be within the general skill of a worker in the art to select a known material on the basis of its suitability for the intended use as a matter of obvious design choice. *In re Leshin*, 125 USPQ 416.

IV. Claims 8 and 15 are rejected under 35 U.S.C. 103(a) as being obvious over Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) in view of Yakovlev et al. (The Journal of Neuroscience, October 1, 1997, 17(19), pages 7415-7424).

Please see Sviri et al. as set forth above.

Sviri et al. differ from the instant invention in not specifically teaching the detection of the marker caspase-3.

However, Yakovlev et al. disclose methods to determine caspase-3 in temporal profiles of apoptosis after brain injury. See abstract. Caspase-3 levels were elevated in brain injury and the inhibition of caspase-3 markedly attenuated apoptosis induced by TBI in vivo and improved neurological recovery. See page 7422, 2nd column. These results may prove the basis for new therapeutic treatments of CNS injury. See page 7423.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate caspase-3 as taught by Yakovlev et al. in the method of Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) because Yakovlev et al. taught that caspase-3 levels were elevated in brain injury and the inhibition of caspase-3 markedly attenuated apoptosis induced by TBI in vivo and improved neurological recovery. See page 7422, 2nd column. These results may prove the basis for new therapeutic treatments of CNS injury. See page 7423.

V. Claims 11 and 15 are rejected under 35 U.S.C. 103(a) as being obvious over Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) in view of Greenberg (Drug News and Perspectives, 1998, Vol.11, No.5, pages 265-270. Abstract Only).

Please see Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) as set forth above.

Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) differ from the instant invention in not specifically teaching the detection of the marker VEGF.

However, Greenberg discloses that stroke results from focal cerebral ischemia due to the occlusion of cerebral blood vessels (angiogenesis). Greenberg further teaches that VEGF is a key mediator of angiogenesis and cerebral ischemia. The understanding of VEGF may have implications for prognosis and treatment in stroke. See abstract.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate VEGF as taught by Greenberg in the method of Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) because Greenberg taught that that VEGF is a key mediator of angiogenesis and cerebral ischemia. The understanding of VEGF may have implications for prognosis and treatment in stroke. See abstract.

VI. Claim 18 is rejected under 35 U.S.C. 103(a) as being obvious over Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) in view of Greenberg (Drug News and Perspectives, 1998, Vol.11, No.5, pages 265-270. Abstract Only), Ronn et al. (WO 00/18801), and Yakovlev et al. (The Journal of Neuroscience, October 1, 1997, 17(19), pages 7415-7424).

Please Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) as set forth above.

Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) differ from the instant invention in not specifically teaching the detection of the a plurality of markers comprising VEGF, NCAM, and caspase-3.

However, Greenberg (Drug News and Perspectives, 1998, Vol.11, No.5, pages 265-270. Abstract Only), Ronn et al. (WO 00/18801), and Yakovlev et al. (The Journal of Neuroscience, October 1, 1997, 17(19), pages 7415-7424) teach the use of the respective markers in stroke and/or cerebral injuries. Please see detailed discussion of Greenberg (Drug News and Perspectives, 1998, Vol.11, No.5, pages 265-270. Abstract Only), Ronn et al. (WO 00/18801), and Yakovlev et al. (The Journal of Neuroscience, October 1, 1997, 17(19), pages 7415-7424) as explained in the rejection of claims 5, 8, 11, and 15 above.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate VEGF, NCAM, and caspase-3 as taught by Greenberg (Drug News and Perspectives, 1998, Vol.11, No.5, pages 265-270. Abstract Only), Ronn et al. (WO 00/18801), and Yakovlev et al. (The Journal of Neuroscience, October 1, 1997, 17(19), pages 7415-7424) in the method of Sviri et al. because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

In other words, each of the claimed markers has been shown to have relevance in the measurement of stroke and/or cerebral injury. See the references to Greenberg (Drug News and Perspectives, 1998, Vol.11, No.5, pages 265-270. Abstract Only), Ronn et al. (WO 00/18801), and Yakovlev et al. (The Journal of Neuroscience, October 1, 1997, 17(19), pages 7415-7424). Therefore, absent evidence to the contrary the combination of multiple markers to produce a predictable result is obvious.

VII. Claim 25 is rejected under 35 U.S.C. 103(a) as being obvious over Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) in view of Montaner et al. (Stroke, 2001, Vol.32, pages 1759-1766).

Please see Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) as set forth above.

Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) differ from the instant invention in not specifically teaching the detection of the marker MMP-9.

However, Montaner et al. teach an ELISA (Enzyme Linked Immunoassay) assay for determining MMP-9 in plasma samples of a subject (pages 1760 and 1764). Montaner et al. also disclose the over expression on MMP-9 levels in stroke. See abstract. The study demonstrated an association between MMP-9 over expression and stroke severity, infarct size, and the time and location of MCA (middle cerebral artery) occlusion.

The researchers taught that "these findings suggest a deleterious role for MMP-9 in the development of brain damage after human ischemic stroke". See page 1765, 2nd column. Further, the ELISA measurements of MMPs for stroke patients seem to be a good tool for research. See page 1765 ,1st column last paragraph.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate MMP-9 as taught by Montaner et al. in the method of Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) because Montaner et al. demonstrated an association between MMP-9 over expression and stroke severity, infarct size, and the time and location of MCA (middle cerebral artery) occlusion.

One of ordinary skill in the art would have been motivated to utilize MMP-9 in stroke measurements because Montaner et al. taught that ELISA measurements of MMPs for stroke patients seem to be a good tool for research. See page 1765 ,1st column last paragraph. As well as the deleterious role of MMP-9 in the development of brain damage after human ischemic stroke. See page 1765, 2nd column.

VIII. Claim 26 is rejected under 35 U.S.C. 103(a) as being obvious over Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) in view of Liu et al. (Thrombosis Research, 1993, Vol.72, No.4, pages 353-358, Abstract Only).

Please see Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) as set forth above.

Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) differ from the instant invention in not specifically teaching the detection of the vWF.

However, Liu et al. teach the measurement of plasma von Willebrand factor (vWF) levels in the acute phase of thrombotic and hemorrhagic stroke prior to therapy. The results showed that vWF levels are increased in both thrombotic and hemorrhagic stroke, and vWF and antithrombin III levels differ between thrombotic and hemorrhagic stroke in patients with high incidence of atherosclerosis. See abstract.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate vWF as taught by Liu et al. in the method of Sviri et al. (Stroke, 1/2000, Vol.31, pages 118-122) because Liu et al. demonstrated that vWF levels are increased in both thrombotic and hemorrhagic stroke.

Therefore, the claim would have been obvious because the substitution of one known element (marker) for another would have yielded predictable results (correlation to stroke) to one of ordinary skill in the art the time of the invention.

8. For reasons aforementioned, no claims are allowed.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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